

# Overt and non-overt disseminated intravascular coagulation and the potential role of heparin in the COVID-19 pandemic outbreak

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**Keywords:** COVID-19, coagulation, DIC, heparin

## Introduction

From December 2019 to date, the sudden outbreak of the coronavirus disease (COVID-19), caused by the transmission of a novel coronavirus known as SARS-CoV-2 induced pneumonia, has led to over 7,912,981 diagnosed cases including more than 433,394 deaths worldwide (15 June 2020, <https://coronavirus.jhu.edu/map.html>). Given the severity of the COVID-19 outbreak all over the world, on 11 March 2020 the World Health Organization (WHO) declared it a global pandemic.

The main clinical manifestations of COVID-19 range from mild upper respiratory tract infection, commonly associated with fever, cough, shortness of breath, fatigue, headache, sore throat, rhinorrhea, and chest pain, through to severe acute respiratory distress syndrome and sepsis.<sup>1</sup> However, despite COVID-19 being primarily manifested as a respiratory tract infection, several data have indicated that it presents a systemic disease involving multiple systems including the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic and immune systems.<sup>2-4</sup> This aspect was also confirmed by abnormalities present in different hematological parameters accompanying the clinical manifestations of COVID-19 infection.<sup>5-13</sup> Specific changes in the number and level of different blood cells were reported by several authors.<sup>5-13</sup> A decrease in lymphocytes and platelets associated with an increase of leukocytes and neutrophils were seen in the majority of the studies.<sup>5-10</sup> A reduction of albumin and

an increase in the amount of glucose, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, creatine kinase, serum procalcitonin, high-sensitivity troponin I, interleukin (IL)-6, serum ferritin, C-reactive protein, and D-dimer were also detected in most patients with COVID-19.<sup>8-11</sup> Supplementary studies have also highlighted that severe COVID-19 infection is often associated and complicated by coagulopathy.<sup>11-16</sup> Thrombocytopenia, prolonged prothrombin time and activated partial thromboplastin time, reduced fibrinogen, elevated D-dimer, and elevated fibrin degradation products were detected in these patients with COVID-19.<sup>11-16</sup> Connors *et al.* reviewing the data on coagulation abnormalities that occur in patients with COVID-19 suggested that this association is a consequence of the inflammatory response to SARS-CoV-2 infection that leads to thrombo-inflammation and drives thrombosis.<sup>15</sup> In fact, patients with coagulation abnormalities showed a higher prevalence (~25%) of venous thromboembolism (VTE) events in addition to pulmonary congestion with microvascular thrombosis.<sup>6,13,17</sup> However, it should be noted that the occurrence of VTE and microvascular thrombosis in patients with COVID-19 is probably underestimated since the admission to contrast-enhanced computed tomography (CT) may be restricted to severely ill patients for practical reasons. In addition, in the pre-COVID-19 era, patients affected by pulmonary embolism also evidenced deep vein thrombosis in the lower limbs.<sup>18,19</sup> On the contrary, in patients with COVID-19 deep vein thrombosis is present in a

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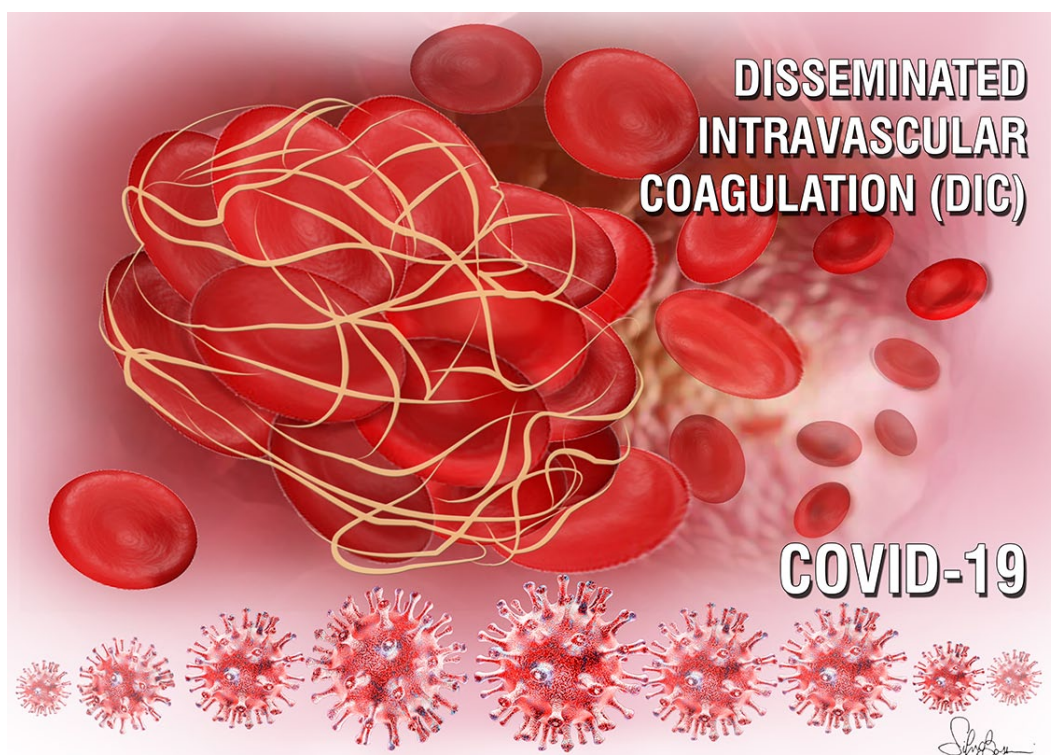
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**Figure 1.** Disseminated intravascular coagulation. COVID-19, coronavirus disease; DIC, disseminated intravascular coagulation.

minority of patients, and pulmonary microthrombi are the result of local hypercoagulation rather than secondary to embolization from the lower limbs.<sup>20</sup> Patients requiring intensive care could then develop venous thrombosis, which can then embolize to the lungs, further aggravating the lung dysfunction.<sup>20</sup> Despite literature data demonstrating that older people (prevalently men) and those with comorbidities, usually cardiovascular diseases, are more prone to this hypercoagulation status during COVID-19, it was observed that younger people, without major underlying diseases, may also present potentially lethal complications such as hypercoagulability with related thrombosis in small and midsize vessels.<sup>13</sup> This hypercoagulation status includes a spectrum ranging from minimal activity that can only be detected by highly sensitive tests for molecular markers of coagulation activation to stronger activation, which includes a consumption of platelets and coagulation factors.<sup>21</sup> In the most serious form, the presence of this hypercoagulable status leads to an inadequate blood supply to different organs thus contributing to multiple organ

failure/dysfunction, giving rise to overt disseminated intravascular coagulation (DIC) disease (Figure 1).<sup>13–16</sup> Several data showed that patients with severe COVID-19 who did not survive may meet the criteria for overt DIC, evidencing that this form of DIC is a strong predictor of mortality in patients developing pneumonia.<sup>13–16</sup> However, currently it is unknown whether the overt DIC described in patients with severe COVID-19 is preceded by a less evident phase of non-overt coagulopathy. Non-overt DIC is defined as subtle hemostatic dysfunction that has not yet reached the decompensation stage as in overt DIC.<sup>22,23</sup> The screening and diagnosis of non-overt DIC in patients with mild/moderate COVID-19 disease could be of key importance in order to optimize treatment and also prevent the organ failure representative of the most severe form of COVID-19. To date, DIC treatment has focused on the primary pathology that causes the coagulopathy, while in the case of COVID-19 infection treatments are still very limited and uncertain, until more can be learnt about the new pathogen.<sup>22,23</sup> Thus, the purpose

of this Letter is to provide a rapid overview on overt and/or non-overt DIC in patients with COVID-19, and also to discuss the potential role of heparin.

### Overt and non-overt DIC in the COVID-19 pandemic

DIC is typified by systemic blood coagulation hyperactivation that leads to the consumption of platelets and coagulation factors, potentially resulting in severe bleeding. Fibrinolytic activity depression and fibrin deposition take place in the microcirculation, leading to multiple organ failure. Since from the beginning of the pandemic, several studies underlined the presence of DIC in patients with COVID-19 an interim guidance for risk stratification of coagulopathy in patients with COVID-19 has been provided by the International Society of Thrombosis and Hemostasis (ISTH).<sup>13</sup> The global research community has made an impressive effort in a very short time, but to date, screening and diagnosis of overt and non-overt DIC still represent a challenge in patients with COVID-19. The most common manifestation in patients with COVID-19 with coagulopathy is an increased D-dimer, a modest decrease in platelet count, and a prolongation of the prothrombin time.<sup>14,21,24</sup> The combination of these manifestations is indicative of DIC, although the pattern differs with respect to DIC due to sepsis.<sup>23</sup> In sepsis, the low platelet count is typically more important, and D-dimer concentrations do not reach the high levels present in patients with COVID-19; in fact, most patients do not have an overt DIC according to the ISTH score.<sup>13,23</sup> In patients with COVID-19 with coagulopathy other laboratory abnormalities are present such as increased lactate dehydrogenase and markedly high ferritin levels, the latter suggestive of thrombotic microangiopathy.<sup>25</sup> Taken together, all the evidence suggests that the coagulopathy linked to COVID-19 is a combination of low/moderate grade DIC (non-overt DIC) and localized pulmonary thrombotic microangiopathy, which could have a critical impact on organ dysfunction in patients with severe COVID-19. Currently, it is not clear whether the overt DIC described in patients with severe COVID-19 is preceded by a less apparent form of non-overt coagulopathy.<sup>13</sup> Interestingly, Fard *et al.* showed that only 6.4% of patients with COVID-19 who died completely met DIC criteria based on ISTH score.<sup>19</sup> Nevertheless, a very

recent study evaluating patients with COVID-19 admitted to a non-intensive care unit suggested that only the 6.4% of patients with COVID-19 who died met overt DIC criteria, while the remaining 81.2% satisfied the non-overt DIC criteria.<sup>26</sup> In this context, it is important to underline that, to date, there is no gold standard for the diagnosis of DIC, and no singular score and/or test able to specifically diagnose it, and this is particularly true for non-overt and a milder form of chronic DIC. In fact, non-overt/milder form of chronic DIC is a subclinical hemostatic dysfunction that has not yet reached the decompensation stage and its diagnosis would include additional parameters such as antithrombin, protein C, thrombin-antithrombin complexes, or soluble fibrin monomer complexes that, currently, are not easily available in the emergency setting and that typically are not considered in routine clinical practice.<sup>27</sup> In patients with COVID-19, the non-overt DIC diagnosis can be even more difficult, considering the probable alterations of the hematological parameters caused by the simultaneous hyperinflammatory status and interactions with antiviral and immunosuppressive drugs that are typically employed at the early disease stage. Thus, in these cases, the organ dysfunction may not be diagnosed, leading to the underestimation of a more complex clinical scenario. In addition, other warning signs of non-overt/milder form of chronic DIC, currently underestimated, may also include cutaneous complications, such as bleeding, petechiae, purpura widespread urticaria, chickenpox-like vesicles, and erythematous rash, all manifestations caused by decreased blood flow through the cutaneous microvasculature system leading to deoxygenated blood accumulation in the venous plexus.<sup>27-29</sup> On 12 June 2020, by searching on PubMed for COVID-19 OR COVID-2019 OR severe acute respiratory syndrome coronavirus 2 OR 2019-nCoV OR SARS-CoV-2 OR 2019nCoV OR (Wuhan AND coronavirus) AND (skin OR cutaneous manifestation), we found 141 reports. Despite skin manifestations due to COVID-19 infection being currently reported mostly in case reports and case series, these manifestations could be also linked to a non-overt DIC. Interestingly, as far as we know, the presence of these cutaneous manifestations, despite being similar to cutaneous involvement occurring during common viral infections, have not been previously detected and/or described for other coronaviruses such as

SARS-CoV and MERS-CoV. So, further studies are needed to give insights to the accurate recognition of a non-overt DIC in patients with COVID-19 pneumonia.

To date, beside the score calculation and the measurement of coagulopathy, hematological parameters (prothrombin time, platelet count, D-dimer) could be useful tools for overt and non-overt DIC diagnosis, and even more importantly, for monitoring disease progression and for planning therapeutic options and strategies; the overall clinical assessment of the patient's status is always mandatory.

### Role of heparin in the COVID-19 pandemic

Since, as previously reported, COVID-19 is frequently complicated by coagulopathy and different forms of DIC can occur in patients, an active application of anticoagulants, such as low-molecular-weight heparin (LMWH), for patients with severe COVID-19 has been recommended by some expert consensus in China.<sup>30,31</sup> The effect of heparin, principally LMWH, was retrospectively analyzed in 449 patients with severe COVID-19<sup>32</sup> showing a reduced mortality when coagulopathy was treated with heparin in comparison to patients not treated with heparin. The same authors also detected an increased level of D-dimer associated with an increased mortality in patients not treated with heparin.<sup>32</sup> After this initial report on LMWH, other studies showed that patients treated with heparin had improved coagulation parameters and normalized immunity, evidenced by increased lymphocyte counts and decreased IL-6 levels, and improved oxygenation.<sup>33,34</sup> However, LMWH efficacy remains to be validated, since in patients who do not show higher levels of activation of coagulation its administration seems not to provide any benefits.<sup>30,31</sup> Currently, it is important to underline that other known non-anticoagulant properties of LMWH may be relevant for the treatment of patients with COVID-19, such as: (a) its anti-inflammatory role through the binding with inflammatory cytokines that leads to the inhibition of neutrophil chemotaxis and leukocyte migration; (b) its protective function on the endothelium through the antagonization of histones released from damaged cells during virus invasion; (c) its defensive action on microvascular inflammation and dysfunction in cardiac failure.<sup>35</sup> It should also be noted that in addition to these

anticoagulant and non-anticoagulant properties, the ability of heparin to prevent viral infection, including Coronaviridae, has already been described.<sup>36</sup> Milewska *et al.* also showed that the strongly related glycosaminoglycan member of heparin, that is, heparan sulfate, functions as adhesion receptors for human coronavirus NL63, complementing the action of the angiotensin-converting enzyme 2 protein.<sup>37</sup> This interaction between coronavirus and heparan sulfate proteoglycans is critical, not only for virus binding, but also for virus replication and could also be potentially relevant for COVID-19 infection.<sup>37,38</sup> Explicitly for COVID-19 infection, in a recent study, it was shown that the SARS-CoV-2 Spike S1 protein receptor-binding domain binds to heparin and this binding induces a significant structural change.<sup>39</sup> Moreover, moieties of basic amino acid residues, that form heparin-binding domains, are solvent available on the SARS-CoV-2 S1 receptor-binding domain surface and constitute a continuous patch that is appropriate for heparin binding.<sup>39</sup> Thus, the usefulness of this drug seems to go beyond the well-known role of anticoagulant during DIC, since several data on Coronaviridae, including SARS-CoV-2, seem to suggest a potential role of heparin and/or heparan sulfate in the mechanism of action of the virus.

### Conclusion

Despite the possible involvement of different forms of DIC in COVID-19 infection and the potential beneficial effect of LMWH, it has to be highlighted that further studies on the link between both overt and non-overt DIC and COVID-19 infection are required. Concerning the therapeutic use of LMWH in the presence of the most serious form of systemic activation of coagulation, DIC, or, more generally, for the treatment of specific hematological and/or clinical manifestation in patients with COVID-19, to date, there are still incomplete data and significant uncertainties with regard to safety. Thus, there is an urgent need for randomized studies that evaluate the clinical efficacy and safety of LMWH in patients with COVID-19. Despite the current ongoing pandemic and the complexity related to the management of patients with COVID-19, it is necessary to evaluate all those hematological parameters related to the differential diagnosis of DIC in patients with COVID-19 in order to understand the real link between

COVID-19 and overt or non-overt DIC. Finally, the involvement of various specialists in the evaluation of hematological and clinical manifestations related to COVID-19 could be of critical importance in thoroughly comprehending the involvement of the various forms of DIC in this COVID-19 pandemic outbreak.

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